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## ELECTRONIC LETTER

# Little value from including cousins in individual risk assessment of hereditary breast cancer: a simulation study

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**B**reast cancer is a common disease in women. The lifetime risk of breast cancer is about 1 in 12 in the UK, 1 in 10 in The Netherlands, and 1 in 8 in the USA.<sup>1</sup> The majority of women are affected in the peri- or postmenopausal years: about 75% of all breast cancer cases are diagnosed after the age of 50.<sup>2</sup> In western countries about 5 to 10% of breast cancer is the result of a genetic predisposition. The most important genes that are involved in this genetic predisposition and have been localised are *BRCA1* and *BRCA2*,<sup>3,4</sup> but these genes only explain a small proportion of the aggregation of breast cancer.<sup>5</sup> The lifetime risk of breast and ovarian cancer in *BRCA1* and *BRCA2* mutation carriers is high, and women are generally affected at younger ages. The recent detection of these cancer genes has led to much media attention. As a consequence, an increasing number of women with one or more relatives with breast cancer visits a family cancer clinic with questions about their risk of developing breast cancer. At these clinics the woman's risk of breast cancer based on the family history can be assessed. The aim of this risk assessment is to identify women with a genetic susceptibility and an associated increased risk of developing breast cancer. The individual risk assessment is very important, particularly for the women whose risk of developing breast cancer is deemed to be at least moderately increased, because decisions have to be made about breast surveillance and possibly DNA testing. This leads to an increasing need for accurate prediction methods to assess individual risks of breast cancer.

Current guidelines for risk assessment are often based on the family history of breast cancer in the first and second degree relatives.<sup>6</sup> In the presence of a dominant mutation, and especially in the case of a dominant disorder with complete penetrance at birth, it may be possible to detect the lineage in a pedigree along which a mutation was inherited. The more extended a pedigree is, the easier it is to detect these lineages. Consequently, it can be hypothesised that using additional information on third degree relatives improves the accuracy of risk assessment and may lead to a therapeutic strategy that is more appropriate for the counsellee. However, collecting and incorporating this information may be very time consuming, especially if all pathology reports must be considered. Only if for a sufficient number of counsellees the additional information leads to a more appropriate therapeutic strategy is it worth changing the current guidelines in order to base medical decisions on third degree relatives too. This was evaluated for the counsellees' female cousins by means of a simulation study. This study and the results found are described in this paper. Other third degree relatives were not considered, since these relatives are in general either too young to have been affected by breast cancer or they had died a long time ago, which makes information less reliable.

## METHODS

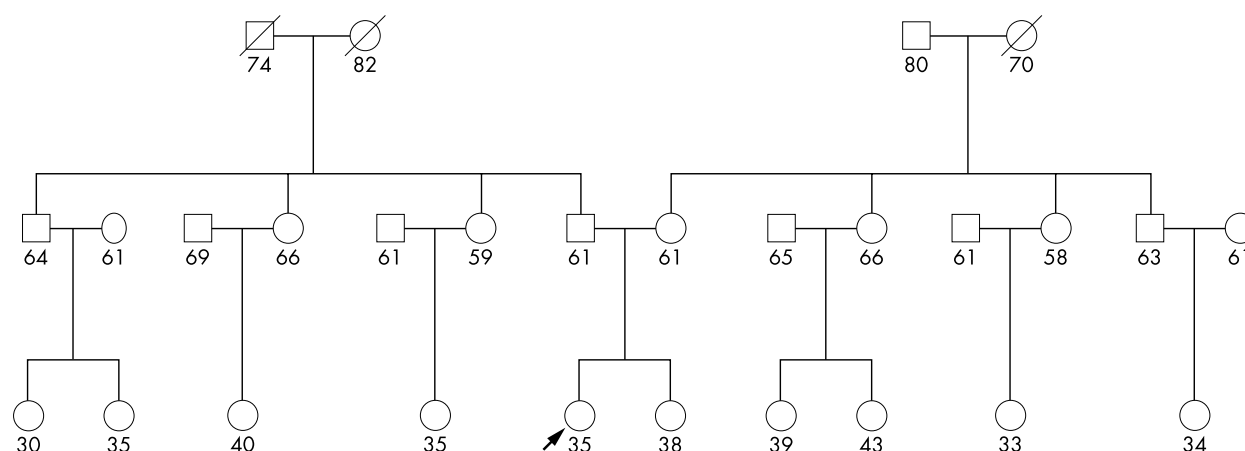
### Pedigree structure

In real life all pedigrees are different and it is impossible to consider all possible pedigrees separately. Therefore the simu-

## Key points

- In family cancer clinics a person's risk of breast cancer is assessed based on the family history of breast and ovarian cancer. These risks are computed in order to decide whether the subject will be offered further diagnosis. Therefore, risk assessment needs to be accurately performed. Risk assessment is often based on the family history of breast and ovarian cancer of first and second degree relatives. In this paper, we studied whether information on cousins improves the accuracy of risk assessment.
- A simulation study was performed. For a chosen pedigree, the genotype and phenotype of all family members were simulated 10 million times. For this simulation, the model presented in Claus *et al* (1991) was used. A selection criterion was used in order to select the pedigrees of which a particular female in the pedigree, the counsellee, visited a family cancer clinic. For each selected pedigree, risk assessment for the counsellee was performed based on her family history of breast cancer including and excluding information on the cousins. The computed risks were evaluated.
- In about 2% of the selected pedigrees, inclusion of information on the cousins led to a different therapeutic strategy for the counsellee. The results are not very sensitive to the pedigree that is chosen and the genetic model that is used.
- Information on the breast cancer history of cousins seldom improves the accuracy of risk assessment and, thus, the additional effort of seeking and incorporating data on the breast cancer history of cousins is not rewarding.

lations were based on one (common) pedigree, which is shown in fig 1. The age is shown for each family member; it is either the current age or the age at death. The choice of the pedigree was mainly based on the counsellees and their families who consult our family cancer clinic.<sup>7</sup> Counsellees are often aged between 30 and 45 years. In the main analysis, the age of the counsellee in the pedigree was therefore taken as equal to 35 years of age. In the sensitivity analysis, a pedigree with a counsellee of 45 years of age was also considered. The counsellee has one sister and eight female cousins. Children of the counsellee in the pedigree are not taken into account, because they would be too young to have developed breast cancer (even if the counsellee is 45 years of age). Male cousins have been excluded from the pedigree, because males are rarely affected by breast cancer at a young age.



**Figure 1** The pedigree used in the simulation study. The age is shown for each family member; it is either the current age or the age at death. The arrow is pointing to the counsellee, the woman whose risk of breast cancer was assessed.

### Model assumptions

For the simulation study the genetic model presented in Claus *et al*<sup>8</sup> was used. In this model, the familial clustering of breast cancer is explained by a dominant mode of inheritance that is represented by one theoretical gene. The mutant allele on this theoretical gene is supposed to be autosomal dominant and the mutant allele frequency was taken as equal to 0.0033. The penetrance function for female carriers is 0.928 times a normal distribution with a mean of 55.435 and a standard deviation of 15.387. For female non-carriers, this curve is 0.100 times a normal distribution with a mean of 68.990 and a standard deviation of 15.387.

### Simulation

The genotype and phenotype of all family members in the pedigree were simulated in two steps. First, the alleles of the single gene for the founders in the pedigree were simulated. The alleles that were simulated were either normal or mutated. The remaining subjects in the pedigree were given alleles by inheriting them from their parents. The alleles, either mutated or not, were inherited independently. Second, given the genotype of a female, her phenotype was simulated whether she would develop breast cancer, and if so at what age. The whole simulation procedure was repeated 10 million times. So, in total, a set with 10 million pedigrees was simulated; each pedigree had its own genotypic and phenotypic combination among the family members in the pedigree.

### Outcomes

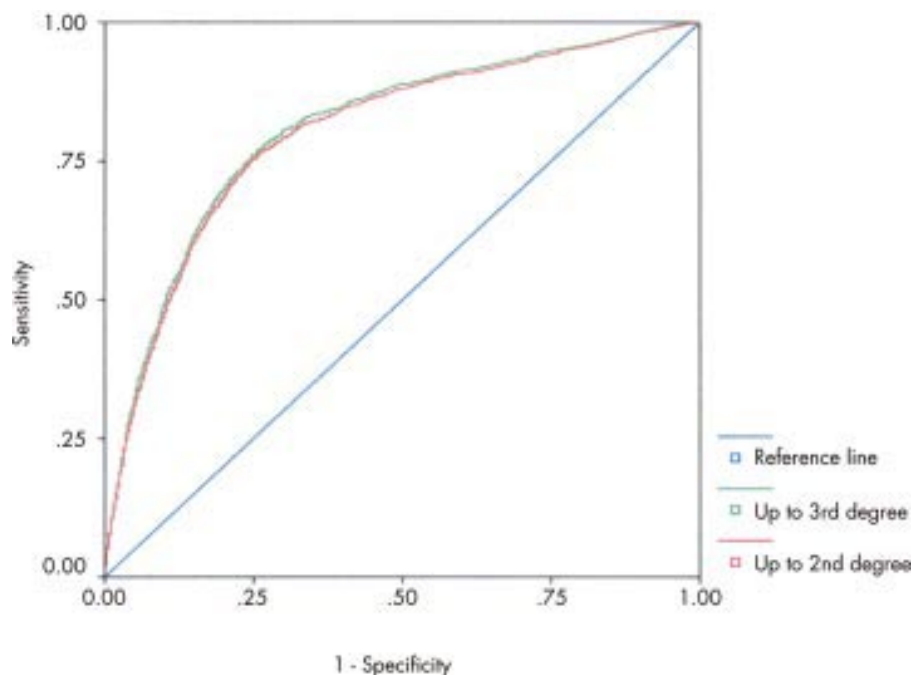
The vast majority of women who visit a clinical genetic centre have questions on the genetic nature of the cancer in their family and on their breast cancer risk<sup>7</sup> (when a woman visits a family cancer clinic for information concerning her daughter's breast cancer risk, this daughter is seen as the counsellee and not the female who visits the clinic). Females who are genetically susceptible to breast cancer are often recognised by the young age (below the age of 50) at which they or family members were affected by breast cancer. The analysis in the simulation study was, therefore, focused on those women who were free of breast cancer and who met the following criterion: the women had at least one first degree relative with breast cancer before the age of 50 or at least two second degree relatives with breast cancer before the age of 50, in the paternal or the maternal family or in both. For all pedigrees that met the inclusion criterion, the counsellee's risk of carrying a mutation and developing breast cancer before the age of 75 was computed twice. The first time the computations were based on the family history of breast cancer up to the second degree relatives. The second time, third degree relatives (the female cousins) were also incorporated into the computations. These computations were carried out in a similar way to Parmigiani *et al*.<sup>9</sup> In these computations, the mutant allele frequency and the penetrance functions given in Claus *et al*<sup>8</sup> were used again. So, the risk assessment yields two outcomes: the counsellee's risk of developing breast cancer before the age of 75 based on her family history up to second and up to third

**Table 1** Counsellees offered further diagnostics when information on cousins was included or excluded from the risk assessment. Number of pedigrees that met one of the inclusion criteria is 183 286 (1.8%)

| Threshold | Risk assessment including or excluding cousins | Number of counsellees referred (%) | Number of mutation carriers among referred counsellees (%) |
|-----------|--|------------------------------------|--|
| 15%       | Exclusive                                      | 55 171 (30.1)                      | 13 585 (24.6)  |
|           | Inclusive                                      | 55 276 (30.2)                      | 13 692 (24.8)  |
| 20%       | Exclusive                                      | 34 983 (19.1)                      | 10 788 (30.8)  |
|           | Inclusive                                      | 34 357 (18.7)                      | 10 847 (31.6)  |
| 30%       | Exclusive                                      | 15 118 (8.25)                      | 6377 (42.2)  |
|           | Inclusive                                      | 15 776 (8.61)                      | 6709 (42.5)  |
| 40%       | Exclusive                                      | 6435 (3.51)                        | 3052 (47.4)  |
|           | Inclusive                                      | 7185 (3.92)                        | 3384 (47.1)  |

**Table 2** Sensitivity and specificity of the two diagnostic tests (for different values of the threshold) based on 183 286 pedigrees that met one of the inclusion criteria

| Threshold | Risk assessment including or excluding cousins | Sensitivity (%) | Specificity (%) |
|-----------|--|-----------------|-----------------|
| 15%       | Exclusive                                      | 75.9            | 74.9            |
|           | Inclusive                                      | 76.5            | 74.9            |
| 20%       | Exclusive                                      | 60.3            | 85.4            |
|           | Inclusive                                      | 60.6            | 85.8            |
| 30%       | Exclusive                                      | 36.6            | 94.7            |
|           | Inclusive                                      | 37.5            | 94.5            |
| 40%       | Exclusive                                      | 17.1            | 98.0            |
|           | Inclusive                                      | 18.9            | 97.7            |



**Figure 2** ROC curves of the two diagnostic tests.

degree relatives. Since the data were simulated, the mutation status of the counsellee was also known.

### Analysis

Counsellees with a cumulative risk of breast cancer above a certain threshold are, in general, referred for further diagnosis. In the analysis, the thresholds 15%, 20%, 30%, and 40% were considered. A threshold of 15% corresponds with a slightly increased risk of breast cancer. The thresholds 20% and 30% are often used to distinguish between low, moderate, and high risk families<sup>10</sup> and a threshold of 40% corresponds with a considerably increased risk. For each threshold, two tables were made. In the first table, the counsellees were classified as to their mutation status and whether they were offered further diagnosis based on their family history of breast cancer up to second degree relatives (diagnostic test up to degree 2). In the second table, the counsellees were classified in a similar way, but the decision about further diagnosis was additionally based on information on the counsellee's female cousins (diagnostic test up to degree 3). The simulated mutation status was taken as a gold standard and for each threshold the sensitivity and specificity were calculated for the two diagnostic tests. Moreover, receiver operator characteristic (ROC) curves were constructed for when the female cousins were included and excluded in the risk assessment (the ROC curve is a plot of the sensitivity versus 1-specificity of a diagnostic test for all possible thresholds for referring a counsellee). Furthermore, the areas under the curves were calculated.

### Sensitivity analyses

To check whether the structure of the pedigree used substantially influenced the results, the analysis was also performed for two pedigrees with a different structure: a small and a large pedigree. These pedigrees were obtained by adjusting the pedigree in fig 1. The small pedigree was obtained by removing the uncle and an aunt from the paternal side and two aunts from the maternal side (including their spouses and their children). The large pedigree was obtained by adding an uncle and an aunt (with spouses) each with two daughters on the paternal side and two uncles (with spouses) also with two daughters each on the maternal side. All cousins included

were 38 years of age. In order to check whether the age of the counsellee and her family members influenced the results, the simulation study was also performed for the pedigree in fig 1 with all ages increased by 10 years. For each of the three pedigrees, the simulation procedure was performed 5 million times and the sensitivity and specificity of the diagnostic tests were computed based on the pedigrees that satisfied the inclusion criterion.

### RESULTS

Of the 10 million simulated pedigrees, 183 286 pedigrees (1.8%) met the selection criterion. In 9.8% of these selected pedigrees, the counsellee carried a mutation. In table 1 it can be seen that the percentages of counsellees referred for further diagnosis and the percentages of mutation carriers among these referred counsellees are merely dependent upon the threshold that is used for referring. Whether or not information on cousins is included in the risk assessment only marginally influences the results. Slightly more mutation carriers would be offered further diagnosis if information on cousins was included. The percentage of pedigrees for which the decision regarding further diagnosis differed in the two situations was very small, between 1% and 2% depending on the threshold used.

Results regarding the sensitivity and specificity of the two diagnostic tests for different values of the threshold are given in table 2. It appears that the changes in sensitivity and specificity are also merely dependent upon the threshold that is used for referring instead of the inclusion and exclusion of information on cousins. The higher the threshold, the lower the sensitivity (that is, the more mutation carriers are missed) and the higher the specificity (that is, the less non-mutation carriers are offered further diagnostic assessment). Fig 2 shows the ROC curves for both diagnostic tests. The curves overlap almost completely. The areas under the two curves equalled 0.80 and 0.81 for the tests where cousins were excluded and included, respectively.

The simulation study was performed for three more pedigrees. For each pedigree the number of counsellees that were referred and the number of mutation carriers among these referred counsellees are presented in table 3. The sensitivity and specificity of the two diagnostic tests for different

**Table 3** Counselees offered further diagnostics when information on cousins was excluded and included from the risk assessment. The numbers of pedigrees that met one of the inclusion criteria are given in the second column

|                | No of pedigrees (%) | Threshold | Risk assessment including or excluding cousins | No of counselees referred (%) | No of mutation carriers among referred counselees (%) |
|----------------|---------------------|-----------|--|-------------------------------|---|
| Small pedigree | 81 749 (1.6%)       | 20%       | Exclusive                                      | 12 304 (15.1)                 | 3607 (29.3)   |
|                |                     |           | Inclusive                                      | 12 396 (15.2)                 | 3667 (29.6)   |
|                |                     | 30%       | Exclusive                                      | 4982 (6.1)                    | 1914 (38.4)   |
|                |                     |           | Inclusive                                      | 5084 (6.2)                    | 1975 (38.8)   |
| Large pedigree | 97 074 (1.9%)       | 20%       | Exclusive                                      | 19 997 (20.6)                 | 5977 (29.9)   |
|                |                     |           | Inclusive                                      | 20 138 (20.7)                 | 6177 (30.7)   |
|                |                     | 30%       | Exclusive                                      | 7701 (7.9)                    | 3230 (41.9)   |
|                |                     |           | Inclusive                                      | 8551 (8.8)                    | 3630 (42.5)   |
| Age + 10       | 124 912 (2.5%)      | 20%       | Exclusive                                      | 16 804 (13.5)                 | 5233 (31.1)   |
|                |                     |           | Inclusive                                      | 17 501 (14.0)                 | 5545 (31.7)   |
|                |                     | 30%       | Exclusive                                      | 9535 (7.6)                    | 3624 (38.0)   |
|                |                     |           | Inclusive                                      | 10 293 (8.2)                  | 3979 (38.7)   |

**Table 4** Sensitivity and specificity of the two diagnostic tests for different pedigrees and for different values of the threshold. The numbers of selected pedigrees that the sensitivity and specificity are based on are given in the first column

|                         | Threshold | Risk assessment including or excluding cousins | Sensitivity (%) | Specificity (%) |
|-------------------------|-----------|--|-----------------|-----------------|
| Small pedigree (81 749) | 20%       | Exclusive                                      | 47.7            | 88.3            |
|                         |           | Inclusive                                      | 48.5            | 88.2            |
|                         | 30%       | Exclusive                                      | 25.3            | 95.9            |
|                         |           | Inclusive                                      | 26.1            | 95.8            |
| Large pedigree (97 074) | 20%       | Exclusive                                      | 60.5            | 83.9            |
|                         |           | Inclusive                                      | 62.6            | 84.0            |
|                         | 30%       | Exclusive                                      | 32.7            | 94.9            |
|                         |           | Inclusive                                      | 36.8            | 94.4            |
| Age + 10 (124 912)      | 20%       | Exclusive                                      | 57.4            | 90.0            |
|                         |           | Inclusive                                      | 60.8            | 89.7            |
|                         | 30%       | Exclusive                                      | 39.7            | 94.9            |
|                         |           | Inclusive                                      | 43.6            | 94.5            |

values of the threshold are given in table 4. Again, the percentage of referred counselees, the percentage of mutation carriers, as well as the sensitivity and specificity merely depend on the structure of the pedigree, the ages of the family members, and the threshold, but hardly on the inclusion or exclusion of the breast cancer history of the cousins. So, the choice of the structure of the pedigree and the ages of the family members in the pedigree did not substantially influence the results.

## DISCUSSION

The decision to proceed with further diagnosis seldom depended on the choice of inclusion or exclusion of information on female cousins in the risk assessment. The sensitivity and specificity of the two diagnostic tests for further assessment based on information on the counsellee's family history of breast cancer including and excluding the counsellee's female cousins slightly differed for each threshold. So, most information is obtained from the first and second degree relatives. The choice of the pedigree structure and the ages of the family members did not substantially affect these results.

The counsellee's cousins are of the same generation as the counsellee and they are therefore also between about 30 and

45 years of age. At their young age they are seldom affected by breast cancer. Only if one or more cousins are affected by breast (or ovarian) cancer and the first and second degree relatives do not give sufficient evidence for the presence of a mutation may the information on the cousins be valuable in risk assessment. This may, for instance, be the case if the counsellee does not have paternal aunts and one or more of her paternal cousins are affected by breast cancer. Such situations are rare. The effort necessary to ask the counsellee about the cancer history of her cousins is minimal. Therefore, an option is to collect information on the cancer history of the cousins by asking the counsellee. Based on the information obtained, it can be decided whether it may be useful to consider pathology reports and to incorporate cousins in risk assessment. The results in this paper showed that this procedure seldom leads to more appropriate advice for the counsellee.

The criterion for including pedigrees in the simulation study probably had no effect on the results. Easing or tightening the criteria would merely affect the number of counselees who would not be offered further assessment, no matter whether cousins are included in the risk assessment or not. The inclusion criteria only concern first and second degree relatives. Females with a clustering of breast cancer among the cousins instead of breast cancer in the first and second degree



relatives may also visit a family cancer clinic for help. However, these situations are rarely encountered in our family cancer clinic and they were therefore not considered.

In the simulation study, the model presented in Claus *et al*<sup>8</sup> was used. In this model, the familial clustering of breast cancer is explained by only one hypothetical gene. Ovarian cancer, bilateral breast cancer, and breast cancer among males are not included in the model. Because the *BRCA1* and *BRCA2* genes are not only involved in genetic breast cancer susceptibility, but also in hereditary ovarian cancer, bilateral breast cancer, and breast cancer among males, it would be of interest to use a genetic model that is based on this information as well. The analysis described in this paper was also carried out for a genetic model with the *BRCA1* and *BRCA2* genes. The mutant allele frequencies for *BRCA1* and *BRCA2* as well as the penetrance functions for mutation carriers were taken as used by Parmigiani *et al*.<sup>9</sup> Ovarian cancer, bilateral breast cancer, and male breast cancer were also modelled as described in the same paper.<sup>9</sup> Similar conclusions to those described above were found (results not shown). Again, only if one or more cousins have had breast or ovarian cancer and the family members in the first and second degree do not give sufficient evidence for the presence of a mutation may the information on the cousins be important in risk assessment. Such situations are rare. The *BRCA1* and *BRCA2* genes only partly explain the family clustering of breast cancer.<sup>5</sup> A genetic model with only these genes systematically underestimates the risk of breast cancer in many pedigrees and is therefore not applicable for risk assessment in family cancer clinics.

In some subpopulations, the mutant allele frequency is considerably higher than in the general population. In order to find out whether the results still hold for these subpopulations, the simulation study as described in this paper was performed for a mutant allele frequency 10 times the mutant allele frequency in the model used before<sup>8</sup>; the new mutant allele frequency equals 0.033. By this change the sensitivities and specificities of the diagnostic tests increase and decrease, respectively. However, the values of these quantities still hardly depend on whether information on the breast cancer history of cousins was included or not. Also, the medical treatment that is offered would be altered if cousins were included in the risk assessment for just a small percentage of the counselees.

The thresholds that are often used in guidelines for further management of counselees are 20% and 30%.<sup>10</sup> A cumulative risk of developing breast cancer of at least 30% is often taken as a threshold for further genetic assessment. This genetic assessment may include DNA testing. A cumulative risk between 20% and 30% is often taken as a threshold for surveillance, like breast self-examination, palpation, and mammography once a year. A cumulative risk under 20% is often used to imply that special interventions will not be cost effective. Therefore, based on the results of the present study it can be concluded that the accuracy of the risk assessment just slightly decreases if information on cousins is not taken into account. For a threshold of 20%, the additional information on the cousins led to a different therapeutic strategy in about 1% of the counselees. This percentage increased to 2% if a threshold of 30% was used. Only some of these cases involve misclassification if information on the cousins is not used in the risk assessment (a pedigree is wrongly classified if either the counsellee carries a mutation

and is not referred for further diagnosis or she does not carry a mutation, but is referred). These wrongly classified pedigrees are difficult to characterise; no difference in the phenotype of the family members in pedigrees of counselees with and without a mutation was found. Similar results hold if other thresholds are used in guidelines to distinguish between low, moderate, and high risk families.<sup>11</sup>

The results in this paper show that in general the additional effort of systematically collecting and incorporating information on the breast cancer history of cousins in family cancer clinics is not rewarding. Only in rare situations does the inclusion of the breast cancer history of cousins in the decision making lead to more appropriate advice for the counsellee. The information on the breast cancer history of cousins is often not very accurate. This even further weakens the argument for seeking and basing medical decisions on the information found. We conclude that cousins do not have to be incorporated in the guidelines for risk assessment.

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